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Gerald A. LoGrippe

Nansie S. Sharpless

Hajime Hayashi

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## DEGREES AND VARIATIONS IN IMMUNOGLOBULIN RESPONSES IN INFECTIOUS HEPATITIS

GERALD A. LOGRIPPO, M.D.\*, NANSIE S. SHARPLESS, M.Sc.\*\*  
AND HAJIME HAYASHI, Ph.D.\*\*\*

### INTRODUCTION

In a previous report, data were presented on an institutional outbreak of infectious hepatitis in children.<sup>1</sup> The purpose of this communication is to detail the *degree* and *variations* of immunoglobulin responses found among hepatitis patients with clinical jaundice, elevated serum transaminase values, or both. These findings put a different light on the complications and chronicity of this disease. In addition, they suggest the potential value of passive immunity in the course of therapy for individuals who are immunologically depressed or incompetent.

### MATERIALS AND METHODS

*Quantitation of Serum Immunoglobulins.* The procedure for determining serum immunoglobulins (Ig) is one developed, standardized and reported from this laboratory.<sup>2</sup> Essentially a micro double-diffusion technic using agar slides, it employs the Ouchterlony principle. Monoimmune antiserum for each of the three immunoglobulins is obtained from commercial sources. The values are expressed in mg/100 ml of serum. The normal adult range of variation (two standard deviations from the mean) for the respective immunoglobulins† are IgA (30-135 mg/100 ml); IgM (40-120 mg/100 ml); and IgG (600-1400 mg/100 ml). The ages of patients in this study are from 1 to 15 years. The normal range of immunoglobulin values for this age group approximates that given for adults. These data are being prepared for publication.

*Qualitation of Immunoglobulin-G.* Serum neutralizing antibody titers to 8-12 enteric viruses were used to determine the quality of IgG. In a previous publication the standards developed for their usage have been described in detail.<sup>4</sup> The enteric viruses also serve to determine whether specific antibodies, present during the acute stage of the disease, decrease four to eightfold or more following 30 to 60 days (half-life or more of IgG turnover) after onset of the disease.<sup>1</sup> (The upper respiratory

\*Chief, Division of Microbiology, Department of Laboratories.

\*\*Technical Assistant, Immunochemistry Section of Microbiology.

\*\*\*Research Associate, Virology Section of Microbiology.

†Nomenclature adopted by WHO Committee, Prague, 1964.<sup>3</sup>

viruses have not been found satisfactory for this purpose since they do not persist throughout the years as do the enteric viruses.<sup>4</sup>) In addition, every effort was made to isolate any virus agent from the individual patients to determine the time sequence for a fourfold sero-conversion and whether antibody titer would develop for the individual's own virus isolate.<sup>1</sup>

*Patient Source:* An acute outbreak of infectious hepatitis occurred at Plymouth State Home and Training School, an institution for mentally retarded children, at Northville, Michigan. Among 652 inmates, 87 children had the clinical signs and symptoms of infectious hepatitis. However, inadequate serum collection and serum volume for immunoglobulin determinations limited this report to 64 cases. Among these, all but nine children had clinical jaundice, elevated serum glutamic pyruvic transaminase (SGPT), or both. The nine patients were included in the evaluation because of their signs and symptoms and the degree of immunoglobulin responses, which were consistently elevated. It should be made clear that the six cases with immunodepression (Table 2) are not among the nine who had no record of jaundice or transaminase values.

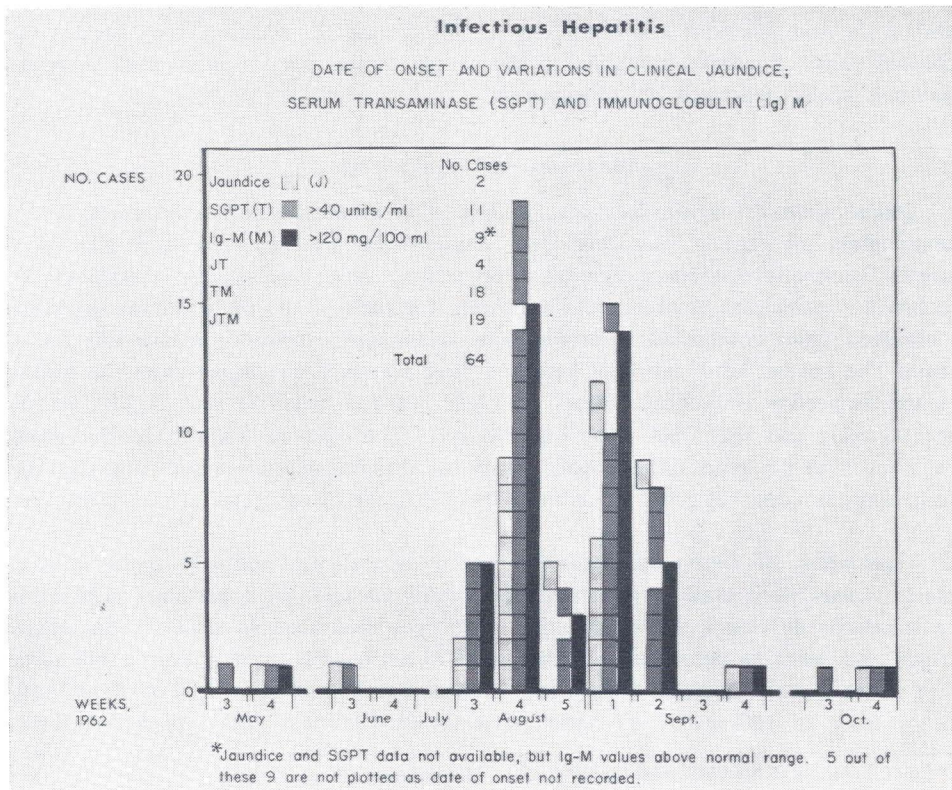


Figure 1

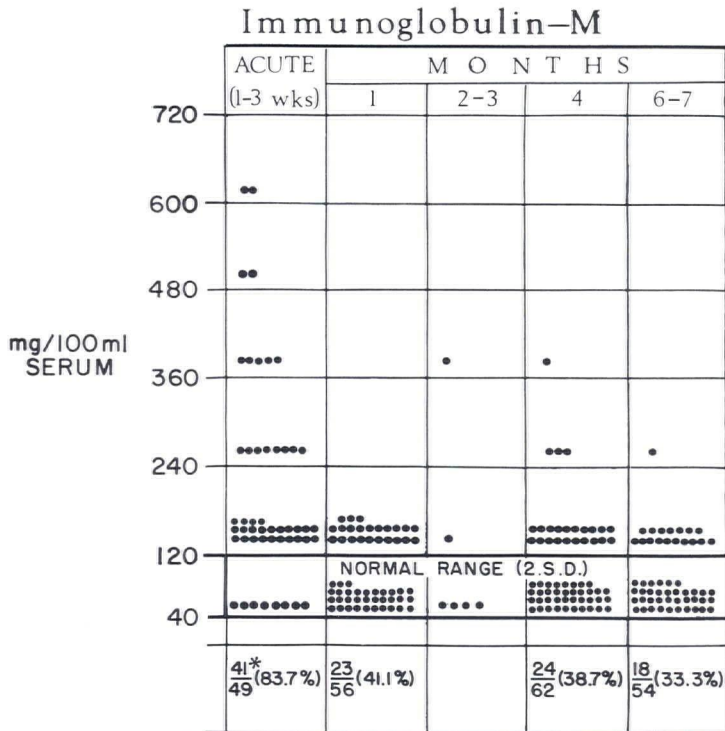
## INFECTIOUS HEPATITIS

### RESULTS

Considerable variation exists in the total number of patients included in the different statistical analyses of the results, because serum was not available on all the patients for all four periods of study. Only those patients were included on whom serum evaluations were available for at least three of the four periods. The majority of patients, however, had serum evaluations for all four periods of study. Excluded from the report were patients who had only one or two evaluations.

The abruptness of the outbreak of infectious hepatitis and the variations in individual responses is shown in Figure 1. The manifestations of clinical jaundice and serum glutamic pyruvic transaminase (SGPT) elevations in relation to the immunoglobulin-M responses are emphasized. Two cases had records of jaundice without transaminase elevations or IgM response; 11 cases showed elevated SGPT only; 4 showed jaundice with elevated SGPT; 18 showed elevated SGPT and elevated IgM;

#### DEGREE OF IMMUNOGLOBULIN RESPONSE IN CHILDREN WITH INFECTIOUS HEPATITIS ( 6-7 month study )



\* NUMERATOR - NUMBER OF CASES ABOVE STANDARD VALUES  
DENOMINATOR - NUMBER SERUM SPECIMENS ASSAYED

Figure 2

19 demonstrated elevated SGPT, elevated IgM, and jaundice. Nine demonstrated elevated IgM with clinical signs and symptoms of hepatitis, but no data were available on SGPT levels or possible jaundice. The fact that the majority of the cases occurred during a four-week period, August 24th to September 14th, supports the concept of a common etiological agent.

Values for the three major classes of immunoglobulins (IgA, IgM and IgG) were determined for all the patients by immunochemical analysis.<sup>2</sup> Since IgA was not significantly altered in any of the patients during the six-month period of study, these values are not included in this report. The degree of IgM response over the entire period is shown in a scattergram (Figure 2). The normal range (2 standard deviations from the mean) for IgM is between 40-120 mg/100 ml of serum. The IgM values are highest during the acute stage of the disease, 83% of the cases showing an elevation above 2 S.D. of the normal range. Although there were several patients with a very high degree of IgM response, the majority showed an elevation of 100

DEGREE OF IMMUNOGLOBULIN RESPONSE  
IN CHILDREN WITH INFECTIOUS HEPATITIS  
( 6-7 month study )

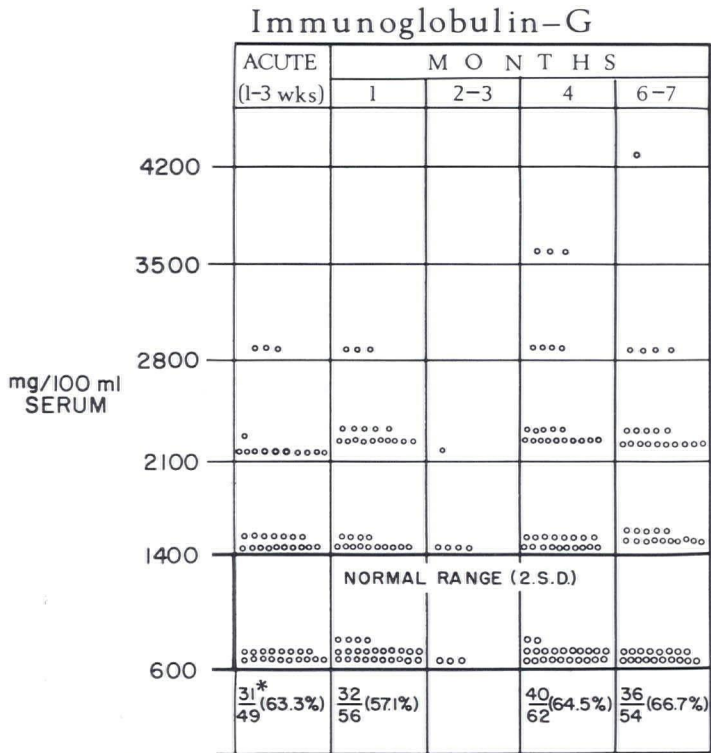


Figure 3

## INFECTIOUS HEPATITIS

to 200% above the 2 S.D. of normal variation. The IgM values are elevated in 41% of the children after the first month; 38% after the fourth month; and 33% after six to seven months. The discrepancy in the total number of cases in each period of study arises from the number of serum specimens available during the different periods.

The *degree of IgG* response is seen in the accompanying scattergram (Figure 3). The overall picture obtained from the data is that, over the six months of study, IgG values which are lowest during the acute stage of the disease gradually increase after 1, 4 and 6-7 months, rising as high as 50% to 150% increase above the normal 2 S.D. range for IgG variations. Also, it is true that in the majority of patients the IgG values rose as the IgM values declined. The totals given at the bottom of the scattergram for each period produce a false impression of a constantly elevated IgG value in the majority of patients, the discrepancy being due again to the number of available specimens.

The *individual variations* in the immunoglobulin responses over the six months of study fall roughly into five groups. Figure 4 illustrates this for IgM. Out of 48 patients, 10 fell into Group A. In these ten cases, the IgM average values were above two standard deviations during the acute stage and they remained elevated at one, four, and six month periods of study. In Group B, 17 patients were found to have IgM average values above two standard deviations during the acute stage,

### Immunoglobulin (Ig) M Response in Acute-Phase and at 1, 4 6-7 months Post Hepatitis

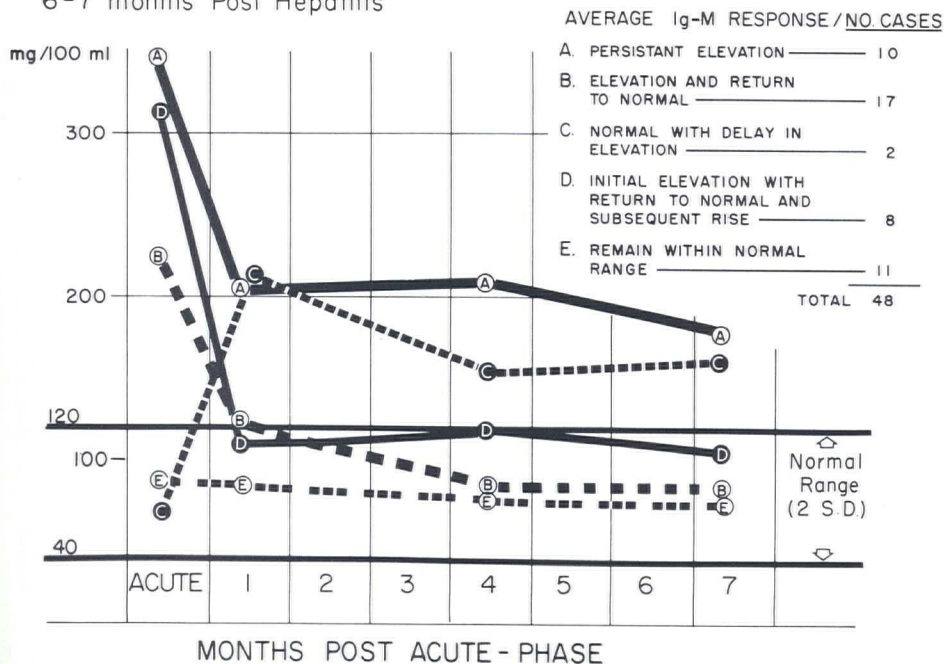


Figure 4

but they returned to normal within one to four months. In Group C, only two patients lagged in their IgM response. However, their IgM values did rise above the two standard deviations within one to four months, and remained elevated at seven months. In Group D, eight patients showed average IgM responses which oscillated from values above two standard deviations to the normal range during the six-month period. In Group E, 11 patients had IgM responses which never did rise above the two standard deviation values.

The relationship of IgG responses to IgM responses is shown in Table I. The five groups of individual responses were also found in the IgG values. To show the true relationship between IgG and IgM responses in detail the following code was devised and used in Table I. The large letters from "A" to "E" represent the groups just described for IgM responses. The small letters from "a" to "e" indicate the same groups of responses for IgG. The arrows indicate immunoglobulin responses above the normal range of two standard deviations. The letter "N" indicates values within the normal range of variation. Any or all of the five IgG probabilities may be found with each of the five IgM groups. The numerals in the squares represent the number of patients showing the type of IgG response associated with the indicated

IgM group. The majority of patients respond with an IgG value indicated by "a" (that group in which the IgG is commonly elevated above two standard deviations during the acute stage of the disease, and remains elevated for at least six months after onset of the disease). This "a" group of IgG responses is, however, spread

TABLE I  
GROUP VARIATIONS OF IMMUNOGLOBULIN (Ig) RESPONSE IN CHILDREN WITH INFECTIOUS HEPATITIS DURING FOUR PERIODS OF STUDY

Gps.	IgM Response*				Patients & IgG Response*					Total Patients
	Acute	Months			"a"	"b"	"c"	"d"	"e"	
		1	4	6-7	↑	↑-N	N-↑	↑↓	N	
A	↑	↑	↑	↑	6	1	1	1	1	10
B	↑	N			9	1	1	1	5	17
C	N	↑	↑		0	0	1	1	0	2
D	↑	N	↑	N↑	5	0	2	1	0	8
E	N	N	N	N	5	0	1	1	4	11
										48

\* ↑ Indicates Ig values above normal range of standard variations (2 S. D.).  
N Indicates Ig values within normal range.

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throughout the five corresponding IgM responses. The other variations do occur in a small number of patients, stressing the individuality of the variation of immunoglobulin responses. The 10 patients listed under IgG column "e" represent a rather large percentage of patients not responding with IgG values of a significantly elevated degree. Here again, the IgG "e" group response is spread throughout the corresponding IgM response groups.

Immuno-depression was demonstrated in 6 of the 64 children studied. Immuno-depression was based on two findings: (a) loss within 1-4 months of significant quantities of specific neutralizing antibodies to enteric viruses present in high titers during the acute stage of the disease; and (b) lack of response with specific serum neutralizing antibodies to active infections of the gastrointestinal tract during the icteric stage which was shown by excretion of live virus in the stool. The effect of infectious hepatitis on antibody response to enteric virus infections as demonstrated in these 6 patients has been published elsewhere.<sup>1</sup> In the present study these 6 patients have been separated into the categories set forth in Table I. The correlation between the categories into which these patients fall and the *variations* and *degrees* of their immunoglobulin responses is shown in Table II. Of the 6 patients, 4 showed no IgM increase during the four periods of study; of the 4 patients, *two* failed to show any IgG increase, *one* demonstrated a delayed increase, which appeared by the fourth period of study, and *one* demonstrated a slight increase in IgG throughout the four periods. Of the remaining two patients, one showed the usual IgM response and an elevation of IgG throughout the four periods of study; the other showed IgM values which oscillated from increased to normal values while the IgG remained markedly elevated during the entire four periods. The varying immunoglobulin responses obtained in these 6 patients with definite immuno-depression emphasize the necessity of determining the quality as well as the quantity of the immune response and the necessity of evaluating each patient individually.

TABLE II  
INFECTIOUS HEPATITIS

Variations and Degrees in Immunoglobulin (Ig) Responses  
in Patients with Immuno Depression

Patient Number	Relationship: IgM to IgG Variations*	STAGE OF HEPATITIS							
		Acute	1 mo.	4 mo.	6-7 mo.	Acute	1 mo.	4 mo.	6-7 mo.
		Ig-M (40-120mg/100ml)**				Ig-G (600-1400mg/100ml)**			
26	E-e	--	97	--	91	--	1,123	--	1,199
31	E-e	78	63	68	--	899	628	848	--
38	E-c	48	--	35	56	1,152	--	1,344	1,730 ↑
51	E-a	64	81	81	72	1,587 ↑	1,920 ↑	1,472 ↑	1,847 ↑
4	B-a	250 ↑	150 ↑	68	79	2,283 ↑	2,182 ↑	1,478 ↑	1,843 ↑
7	D-a	368 ↑	109	125 ↑	120	3,042 ↑	2,906 ↑	3,552 ↑	3,426 ↑

\* Immunologic categories described in Table-I.

\*\* Normal range of variation (mean ± 2 S. D.).



## DISCUSSION

The *degrees and variations of immunoglobulin* responses found among 64 cases of infectious hepatitis offer a new explanation for the complexities of this disease. The large and confusing literature on the complications and sequelae have not been explained on the basis of varying etiological agents, and clinical, laboratory and pathological manifestations. The common denominator may well be the "*immunological status of the individual*" and his specific ability to cope with intercurrent infections and endotoxemias. The degrees and variations in the immunologic status of the individual may now be *quantitated* and *immunoglobulin-G-qualified* as well. It remains to correlate, if possible, these findings with the final outcome of the disease. What is the immunoglobulin response of the patient who recovers completely as contrasted with the immunoglobulin response of the patient who progresses into a chronic state or remains a carrier? In a previous communication<sup>1</sup> it was postulated that the primary disease may well be in the reticuloendothelial system and the damage to the liver secondary to an endotoxemia acquired during an immunodepressive state. The data also showed an immunodepressive state in 10% of the children. It lasted for a period of at least six months (the duration of the study period). The degrees and variations in immunoglobulin responses presented in this paper together with the evidence presented in previous communications<sup>1,4</sup> strongly support the view that the complications and sequelae seen in this disease may not be due to the primary infection *per se* in the liver. They may very well represent a reaction to any number of intercurrent infections and endotoxemic states subsequent to the varying degrees of immunodepression and lack of immune response (globulin dyscrasia).<sup>4</sup> This deficiency can be in the form of the *quantity* or *quality* of the immunoglobulin components, or both, as evidenced from the data presented from this laboratory.<sup>1,4,5</sup>

On the basis of the five variations in IgM responses (Groups A to E) and the related IgG responses shown in Table I, it appears more logical to interpret the clinical complications and sequelae of this disease on the individual's immune status. Although it is tempting to speculate which variety of immune response is responsible for the different complications known, this is not possible with the data available. For example, one cannot postulate whether individuals in the IgM Group A are hepatitis carriers because of a persistence of antigenic stimulation (demonstrated by an elevated IgM), or whether individuals in IgM Group E continue to shed active hepatitis virus (i.e. are carriers) because of an incompetent immune mechanism. In an attempt to explain why IgM persists, one or two possibilities may be postulated: either the IgM stimulation is from the hepatitis virus *per se* or from such stimulants as gram negative endotoxins whose presence is due to an immuno-depressive state of the reticuloendothelial system. However, until the hepatitis agent(s) becomes available as a practical laboratory tool, the variations and degrees of immunoglobulin responses can only be correlated roughly with clinical complications and sequelae associated with the respective responses. Moreover, new methods are required to determine which complications are due to virus action and which are due to intercurrent infections and endotoxins.

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With a better understanding of the immunologic status of the hepatitis patient, justification for passive immunity therapy or prophylaxis is demonstrated. Hepatitis free plasma<sup>6,7,8,9</sup> or gamma globulin should be useful dependent upon whether immunodepression, immunoglobulin deficiency or immunoglobulin dyscrasia is demonstrated; determination of the specific condition being possible with our methods of analysis.

### SUMMARY

Of 87 cases of infectious hepatitis, 64 were studied to correlate the *degrees* and *variations* of immunoglobulin (Ig) responses in serum. The 64 cases were selected on the basis of clinical jaundice, elevated serum glutamic pyruvic transaminase levels above 40 units/ml of serum, or both. IgA values were not significantly affected during the four periods of study. The degree of IgM increases varied from 100% to 600%, and IgG from 50% to 150% above the upper limits of normal values. The immunoglobulin values were compared during the acute stage, and at one, four, and six-to-seven months thereafter. The variations in IgM and IgG responses in hepatitis patients are grouped into five categories: (1) those with persistent elevations beyond seven months; (2) those returning to normal in one to four months; (3) those oscillating between elevated and normal values; (4) those with delayed responses; and (5) those with no rise in IgM or IgG values above the normal range of variation. From the data available it is not possible to come to any predictable conclusion as to the Ig responses in patients with infectious hepatitis. The variations in responses indicate that the immunoglobulin status must be determined on an individual basis. A state of immunodepression in 10% of the patients during the stages of the disease gives rise to interesting speculations, though, here again, no definite conclusions can be reached.

### ACKNOWLEDGMENT

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